The present study aimed at unraveling certain genetic markers associated with RPL of unknown etiology and the results propose a multigeneic model for RPL. It substantiates the concept that no single gene is sufficient to produce disease segregation; rather, disease risk is influenced by several genes and possibly by several gene-gene interactions. Certain genetic profiles brought out in the present study, strongly predict the risk of RPL and these would enable identification of genetically predisposed individuals. The study brings out the significant role of immunomodulation in the maintenance of pregnancy through the identification of certain high risk HLA G and KIR genes. Further the significant roles of genes in vascular remodeling, xenobiotic metabolism and DNA repair towards RPL have been identified.

The salient findings of the immunomodulatory gene polymorphism analysis include:

- Increased frequency of the low secretor HLA G*0105N allele in RPL women and increased sharing of G*0104 allele between the partners. This indicates that the polymorphisms in the HLA G that alter the amino acid sequence play a major role in RPL.
- The HLA G I/D genotype was also found to be significantly higher in RPL women than the controls. The significance of this polymorphism in RPL could be due to its ability to mediate the differential expression of HLA G alleles.
- The KIR genes, 2DP1, 2DL1 and 2DS4 were found in increased frequency in the partners of RPL women.
- A significant difference was observed in the presence of full repertoire of five inhibitory KIR genes between RPL and control men. Further, the percentage of women with RPL who lack inhibitory KIRs possessed by their husband was significantly higher than that of women with successful pregnancies.

The HLA G and KIR effect in pregnancy would involve the cumulative interaction of several inhibiting and activating receptors with a variety of class I molecules appearing on the HLA haplotypes expressed on trophoblast. The confirmation of the role of HLA G and KIR in RPL with future extensive studies will enable genotyping and analysis of
combinations of *HLA G* and *KIR* in aborting couples to be practically applied as a marker to support the diagnosis of the alloimmune etiology of pregnancy loss.

The results of the vascular remodeling gene polymorphism analysis revealed:

- Increased risk associated with VEGF C/A genotype which could be due to the altered VEGF production, resulting in the formation of a vascular network with an abnormally high apoptotic tendency.
- Lack of association of ACE and MTHFR genotypes with RPL.
- However the combination of VEGF C/A genotype with certain ACE and MTHFR genotypes revealed a significant association with RPL indicating the predominant role of VEGF in PRL.

The analysis of the role of xenobiotic metabolism in RPL revealed:

- Increased risk associated with CYP1A1 w1/m1 and GSTM1 -/- genotypes.
- The combination of GSTM1 -/- and GSTT1 +/-; CYP1A1 w1/m1 and the GSTM1 -/- revealed a significant association with RPL.

The presence of these genotypes prevents the removal of oxidative stress that might result from angiogenesis and also lead to increased toxic metabolite accumulation that could form DNA adducts and thus induce DNA damage. Hence it is essential that the DNA repair mechanisms are efficient to prevent the genotoxic effect.

The DNA repair gene polymorphism analysis indicated:

- Increased risk for RPL with XPD Lys/Gln genotype, which could be due to the decreased repair capacity associated with this genotype.

The combined gene-gene interaction analysis highlight the fact that the presence of high risk genotypes in all the pathways predisposes an increased risk and enhanced
susceptibility rather than the presence of a single high risk genotype in anyone of the pathway.

The present study is the first of its kind in South Indians and has proposed susceptibility markers and genotype profiles that attribute to an increased risk of RPL. The genetic susceptibility markers in each of the pathways as well as the gene-gene interaction within each pathway as well as among the genes of the four pathways have been established. Subsequent genetic studies in this arena will unravel additional susceptibility markers and enable a thorough understanding of the etiology of RPL.